REMARKS

Claims 1 to 115 were pending in this application. Claim 1 has been amended without prejudice and without conceding to the Examiner's characterizations. Claims 4, 9, 13, 15, 24, 25, and 30-115 have been withdrawn. Claim 11 has been canceled without prejudice and without conceding to the Examiner's characterizations. Claims 116 and 117 have been added and do not constitute new matter.

The Examiner listed that "claims 30-57, 59-115, 4, 9, 13, 15, 58, 25, 27 are withdrawn from further consideration ...as being drawn to a nonelected invention and species." Applicant believes that claim 27 was incorrectly listed and should be replaced with claim 24. If this is incorrect, kindly contact the attorney by phone.

35 U.S.C. § 102

Pence

Claims 1, 2, 10, 11 and 14 were rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by Pence U.S. Patent No. 3,634,264 ("Pence"). Applicant traverses this rejection for at least the following reasons.

Applicant's claimed invention as amended does not utilize imidazole for the treatment of mite infestations. Pence does not teach sulfur and sulfur derivatives as mitocides, but rather requires that use of "imidazole" to "kill blood-sucking ectoparasites." Col. 1, lines 69-70. Because an additional active ingredient, imidazole, is required by Pence, Applicant's claimed invention is not anticipated. Applicant respectfully asserts that this rejection has been overcome.

Suzuki

The Examiner rejected claims 1, 2, 5-8, 10, 11, 14, 17 and 18 under 35 U.S.C. § 102(b) as being anticipated by Suzuki JP 3-002124 ("Suzuki"). Applicant traverses this rejection for at least the following reasons.

According to the Examiner, "[t]his is the instant method as claimed; the sufficient to treat Mites [sic], if they are present, and prevent their effects, if they are not yet present." However, Applicant's claims require "infestations of cutaneous mites." (Claim 1 requires this and the other rejected claims depend upon claim 1.) There is no teaching in Suzuki to treat infestations of mites, and therefore all of Applicant's claim limitations are not taught, and the invention is not anticipated. Applicant respectfully submits that this rejection has been overcome.

Bhagwat

Claims 1, 10-12, 14, 17-23, 24, 26, 28 and 29 are rejected under 35 U.S.C. § 102(e) as being anticipated by Bhagwat U.S. Patent No. 6,429,231 ("Bhagwat"). Applicant respectfully traverses the rejection for at least the following reasons.

The Examiner states that Bhagwat, "provides the methods as are instantly claimed, without recognizing that the methods would in fact treat mites." Applicant's claimed invention is limited to "treatment of infestations of cutaneous mites." This limitation is not taught by Bhagwat, which uses a composition for "disorders due to microbial infection or changes in normal keratinization, epidermal formation or pilosebaceous function, such as acne, psoriasis, seborrhea, rosacea, ingrown hairs and pseudofolliculitis barbae, and hyperpigmented skin, and cutaneous infection." Col. 1, lines 39-43. An infestation of mites is not synonymous with any of these disorders; a patient with any of these disorders does not necessarily have an infestation of mites, and therefore Bhagwat's methods do not inherently or explicitly anticipate Applicant's claimed inventions. This rejection should be withdrawn.

Harry's

"Claims 1-3, 10-12, 14, 17, and 18 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Harry-73." ("Harry's") According to the Examiner, "[s]ince the compositions are applied to the skin, within which a Mite effective treatment amount is present, then the instant methods are met, as Mites could be the unrecognized bases for the perceived need for use for each of Harry's composition." Applicant traverses this rejection for at least the following reasons.

Suzuki teaches the use of its composition for "prevention and treatment of acne." Suzuki, p. 12. There is no teaching that acne patients necessarily have mite infestations. Without such a teaching, there is no anticipation, inherent or otherwise, because Applicant's claimed invention requires "treatment of infestations of cutaneous mites." The § 102 rejection should be removed.

An additional rejection of obviousness was made by the Examiner and Applicant traverses this rejection for at least the following reasons. 35 U.S.C. § 103 requires a teaching or suggestion to modify the invention as is claimed by Applicant. Mite infestation is a separate skin condition from acne, and Harry's only teaches acne treatment and prevention. Given that acne is attributed to "an interaction among the hormones, keratin, sebum, and bacteria," and not mites (The Merck Manual, Seventeenth Edition (1999), 811-814, attached as Exhibit A), one of ordinary skill in the art would not find it obvious to use an acne treatment for mite infestation. Therefore, Applicant respectfully asserts that this rejection has been overcome.

35 U.S.C. 103

Suzuki or Harry's in view of Bonpar, Lin and Kligman

The Examiner has rejected claims 1-3, 5-8, 10-12, 14 and 16-20 under 35 U.S.C. § 103(a) as being unpatentable over Suzuki or Harry's in view of Bonnar, Lin and Kligman U.S. Patent No. 4,752,472. Applicant traverses this rejection for at least the following reasons.

Applicant reasserts the reasons why neither Suzuki nor Harry's does not teach Applicant's claimed invention, i.e. neither reference teaches the treatment of infestations of mites. The Examiner notes that Lin teaches "sulfur use, including 10% sulfacetamide preparations to control Demodex," however this is incorrect. Lin in Table III teaches only that sulfur may be useful in Demodectic eruptions, and says nothing about the use of sulfur derivatives (including sodium sulfacetamide) for Demodex (mites). Table IV does not list any composition for the treatment of mites, and the disorders which are treated by these compositions (acne, dandruff, etc.) have different etiologies.

According to the Examiner, Kligman "show[s] Demodex present in cutaneous disorders treated as by the cited art." However, Kligman merely states "other retention products such as bacteria (P. acnes) fungi (P.ovale) and a mite (Demodex folliculorum) contribute to the follicular debris." Kligman, col. 1, lines 30-33. Nowhere does Kligman teach or suggest that this debris is correlated with the "cutaneous disorders treated by the cited art," as alleged by the Examiner.

The Examiner tries to equate treatment of skin disorders in general with the treatment of mites because "Bonnar shows they are always present on people." However, not all people have infestations of mites. *See* Marks, Histopathology of Rosacea, Arch. Derm., vol. 100, Dec. 1969 p. 683-691 (a copy is attached as Exhibit B). While Bonnar states, "Increased mites may play a part in the pathogenesis of rosacea," (Bonnar, p. 443, emphasis added) it is now known that not all rosacea patients have infestations of mites, and therefore mite infestation is a problem distinct from rosacea. Marks states, "The finding of Demodex in only

19% of our biopsy material [from rosacea patients] and its absence from areas of inflammation in sections in which it was found are much against a significant role for this organism in this disease [rosacea]." Marks, 690. Therefore, use of sulfur on skin disorders not related to mite infestations in the cited art does not teach or suggest using sulfur and sulfur derivatives for treatment of mite infestations, and Applicant's claimed invention is not rendered obvious. Applicant respectfully submits that this rejection has been overcome.

CONCLUSION

Applicant respectfully submits that the application is in condition for allowance.

Applicant does not believe any additional fee is required for this Response and Request for Reconsideration, however, in the event any additional fee is required or any overpayment credit is due, the Commissioner is hereby authorized to charge Deposit Account No. 18-0586.

I hereby certify that this paper and the papers referred to herein as being transmitted, submitted, or enclosed herewith in connection with U.S. Serial No. 10/022,476 is/are being facsimile transmitted to the United States Patent and Trademark Office fax number 703 872-9306 on the date shown below.

Maryellen Feehery

12/8/03

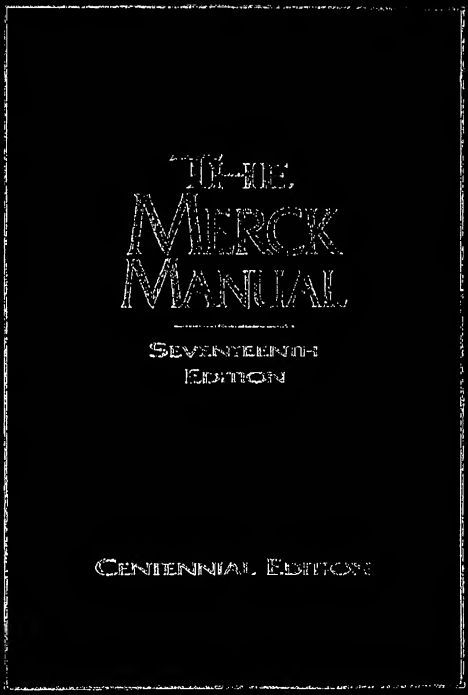
Date of Facsimile Transmission

Respectfully submitted,
REED SMITH LLP

Maryellen Feehery
Registration No. 44,677
William J. McNichol, Jr.
Registration No. 31,179
2500 One Liberty Place
1650 Market Street
Philadelphia, PA 19103-7301
(215) 241-7988

Attorneys for Applicant

EXHIBIT A


THE
MERCK
MANUAL
SEVENTEENTH
EDITION
CENTENNIAL EDITION

Editorial and Production Staff

Executive Editor: Keryn A.G. Lane

Senior Staff Editor: Susan T. Schindler
Staff Editor: Julie Kosteeky
Staff Editor: Sandra J. Masse
Production Editor: Debra G. Share
Contributing Editor: Roger I. Schreck, M.D.

Designer: Lorraine B. Kilmer
Indexer: Susan Thomas, Ph.D.
Textbook Production Coordinator: Diane C. Zenker
Medical Textbook Coordinator: Dorothy A. Bailey
Executive Assistant: Diane Cosner-Bobrin

Publisher: Gary Zelko
Advertising and Promotional Supervisor: Pamela J. Barnes

Library of Congress Catalog Card Number 1-31760
ISBN 091910-10-7
ISSN 0076-6526

First printing—January 1999
Second printing—June 1999

Printed in the U.S.A.

FOREWORD

With this edition, *The Merck Manual* celebrates its 100th birthday. When the editors of the 1st Edition produced their 192-page compendium, they could not have realized the extent to which medical knowledge would explode over the next century. *The Merck Manual* now fills 2,655 pages and covers countless diseases that were not known 100 years ago. A brief review of medical practice as reflected in *The Merck Manual* during the past century follows on page vii.

Although the knowledge of medicine has grown, the goal of *The Merck Manual* has not changed—To provide useful clinical information to practicing physicians, medical students, interns, residents, nurses, pharmacists, and other health care professionals in a concise, complete, and accurate manner. *The Merck Manual* continues to cover all the subjects expected in a textbook of internal medicine as well as detailed information on pediatrics, psychiatry, obstetrics, gynecology, dermatology, pharmacology, ophthalmology, otolaryngology, and a number of special subjects. *The Merck Manual* quickly provides information that helps practitioners achieve optimal care. The more specialized the practice of medicine becomes, the more important such information becomes. Specialists as well as generalists must at some time quickly access information about other specialties.

The 17th edition of *The Merck Manual* is the culmination of an arduous but rewarding 7-year enterprise. Every topic has been updated, and many have been completely rewritten. Topics new to this edition include hand disorders, prion diseases, death and dying, probabilities in clinical medicine, multiple chemical sensitivity, chronic fatigue syndrome, rehabilitation, smoking cessation, and drug therapy in the elderly, among others. The members of the Editorial Board, special consultants, and contributing authors are listed on the following pages with their affiliations. They deserve a degree of gratitude that cannot be adequately expressed here, but we know they will feel sufficiently rewarded if their efforts serve your needs.

Because of the extensive subject matter covered and a successful tradition developed through trials of successes and failures, *The Merck Manual* has some unique characteristics. We urge readers to spend a few minutes reviewing the Guide for Readers (p. xii), the Table of Contents at the beginning of each section (indicated by a thumb tab), and the Index (p. 2557). Subject headings within each section, internal headings within a subject discussion, and boldfaced terms in the text form an outline intended to help with use of the text.

We hope this edition of *The Merck Manual* will serve as an aid to you, our readers, compatible with your needs and worthy of frequent use. Suggestions for improvements will be warmly welcomed and carefully considered.

MARK H. BEERS, M.D., and ROBERT BERKOW, M.D., *Editors*

OF WART VIRUS AND CLINICAL CORRELATIONS

Human Papillomavirus Type	Clinical Correlations
2, 4, 7	Benign
10	Benign
11	Of women, 28% have associated cervical dysplasia with koilocytic cells
, 18, 33	Found in > 60% of tumors in women with invasive carcinoma of cervix; type 16 is found in 80% of men and women with bowenoid papulosis of external genitalia; lesions usually disappear spontaneously, but future cancers may appear
b, c, d, e	Buschke-Löwenstein giant condyloma is often malignant; also found in cervical dysplasia and laryngeal tumors
ıny from 34–58	Most are associated with cervical intraepithelial neoplasia (see Ch. 24)
10	Common warts; usually benign
b; 8	Often malignant; sunlight and x-ray therapy are cofactors, especially with type 5
4, 7, 9, 10, 12, 14, 17–19, 20, 23–25	Most seem benign, except possibly 14, 17, and 20
ır others	Often malignant; sunlight is a cofactor
11, 16, 30	May become malignant; may occur in infants on passage through the vaginal canal and in adults as a consequence of oral-genital sex; may spread to lungs as cancer
	Benign

le) or a 5% ided sequen- fluorouracil . to treat flat may follow lesions.

ı long-term ın are avail- injection of bleomycin s and cures , reports of

Raynaud's phenomenon and vascular damage of fingers where warts have been injected with bleomycin warrant extreme caution despite the popularity and effectiveness of this technique among some experts.

Extensive warts, even in hitherto untreatable epidermodysplasia verruciformis, have improved or cleared with oral isotretinoin or etretinate, which must be used by physicians familiar with these drugs and their possible adverse effects, especially fetal abnormalities during pregnancy.

Interferon, especially interferon-α, intralesionally (3 times/wk for 3 to 5 wk) or IM, has also cleared intractable skin and genital warts.

MOLLUSCUM CONTAGIOSUM

A poxvirus infection characterized by skin-colored, smooth, waxy, umbilicated papules 2 to 10 mm in diameter.

Transmission, often venereal, is by direct contact. Numerous small papules may appear anywhere on the skin, often in the genital and pubic area. The lesions are usually asymptomatic, unless secondarily infected, and may be discovered when the patient is examined for a sexually transmitted disease.

Lesions can be diagnosed easily by the characteristic central umbilication or dell, filled with a semisolid white material that, if expressed and Giemsa-stained, shows inclusion bodies within many large cells or extracellularly. The disease can spread by autoinoculation but, after months, may disappear spontaneously. A giant molluscum may grow to two or three times its original diameter. Eczematous dermatitis may surround several molluscs, especially in young children; the cause is unknown.

Successful treatment usually requires destroying each lesion by freezing; by removing the central core of the papule with a needle, a comedo extractor, or the tip of a #11 scalpel blade; or by trichloracetic acid application (25 to 40% solution).

116 / DISORDERS OF HAIR FOLLICLES AND SEBACEOUS GLANDS

ACNE

A common inflammatory disease of the pilosebaceous glands characterized by comedones, papules, pustules, inflamed nodules, superficial pus-filled cysts, and (in extreme cases) canalizing and deep, inflamed, sometimes purulent sacs.

Pathogenesis

An interaction among hormones, keratin, sebum, and bacteria determines the course and severity. Acne usually begins at puberty, when an increase in androgens causes an increase in the size and activity of pilosebaceous glands. Inflammatory acne lesions include papules, pustules, and nodules or cysts. Noninflammatory lesions include open and closed comedones (ie, blackheads and whiteheads). First, intrafollicular hyperkeratosis leads to blockage of the pilosebaceous follicle; consequently, comedones form, composed of sebum, keratin, and microorganisms, particularly *Propionibacterium acnes*. Lipases from *P. acnes* break down triglycerides in the sebum to free fatty acids (FFA), which irritate the follicular wall. Retention of sebaceous secretions and dilation of the follicle may lead to cyst formation. Rupture of the follicle, with release into the tissues of FFA, bacterial products, and keratin, induces an inflammatory reaction that usually results in an abscess. These abscesses heal, with scarring in severe cases. Acne usually spontaneously remits, but the time of remittence cannot be predicted.

Symptoms and Signs

Acne is often worse in winter and improved in summer, probably because of the benefits of sunlight. Diet has little effect; however, if a food is suspected, it should be omitted for several weeks and then eaten in substantial quantities to determine if acne worsens. Acne may cycle with the menses, and it may improve or worsen during pregnancy. Although cosmetics rarely aggravate acne, the traditional advice to avoid greasy preparations seems prudent.

Superficial acne: Blackheads (open comedones) or whiteheads (closed come-

dones), inflamed papules, pustules, and superficial cysts are characteristic. Large cysts occur occasionally, sometimes after manipulation or trauma to an otherwise uninflamed blackhead. The prognosis for healing without scars is good in superficial acne, but attempts to extrude blackheads or superficial cysts and scratching of ruptured lesions may increase scarring.

Deep acne: This form is characterized by the above findings with deep inflamed nodules and pus-filled cysts, which often rupture and become abscesses. Some of the abscesses open on the skin surface and discharge their contents. Lesions are most common on the face, but the neck, chest, upper back, and shoulders may also be affected. Scarring is frequent.

Diagnosis

Comedones are almost always present, and lesions at various stages of development are seen simultaneously. Differential diagnosis includes rosacea, which does not have comedones, and corticosteroid-induced acneiform lesions, which usually have follicular pustules in the same stage of development and no comedones.

Treatment

Although acne is almost universal, it may embarrass adolescents, who may withdraw, using the acne as an excuse to avoid difficult personal adjustments. Supportive counseling for patients and parents may be needed. Misconceptions about a relationship between acne and diet, athletics, or sex are common and warrant discussion. Treatment depends on the severity of the lesions.

Superficial acne: Although washing lesions several times a day has little effect, the appearance of an oily face often improves. Any good toilet soap may be used. Antibacterial soaps are of no benefit, and irritation from abrasive soaps makes it difficult to use follicular drugs (see below).

In **superficial pustular acne,** topical clindamycin or erythromycin alone or with one of the follicular drugs mentioned below is probably most useful. Sunlight causes mild dryness and slight scaling and is usually helpful. However, sunlight is not always available, and its benefit may be difficult to duplicate with a sunlamp. Azelaic acid cream 20%, which has antiproliferative and antibacterial effects, may be effective in comedonal or inflammatory acne.

Topical tretinoin (retinoic acid) in 0.025% 0.05%, or 0.1% cream, 0.05% liquid, or 0.01% or 0.025% gel is also often effective. A new topical retinoid, adapalene 0.1% gel, was recently approved in the USA. It may be slightly less irritating than topical tretinoin. These retinoids must be applied carefully and at night (every other night if irritation is excessive), going over the entire affected area only once. The eyes, nasolabial folds, and creases of the mouth should be avoided. The liquid form of tretinoin should be applied with a cotton-tipped applicator. Exposure to sunlight and use of other drugs are restricted to prevent severe irritation. With tretinoin or adapalene, acne may worsen at first; improvement usually requires ≥ 3 to 4 wk.

Other topical drugs include 5% to 10% benzoyl peroxide, OTC drugs, and various sulfur-resorcinol combinations; they are usually applied twice daily or on preparation at night and another in the morning. Oral antibiotics may also be helpful in superficial pustular acne.

Deep acne: Vigorous management is required to reduce residual scarring. For severe, deep lesions, topical treatment is unsatisfactory; a broad-spectrum oral **antibiotic** is usually effective because it reduces bacterial organisms. The most cost-effective is tetracycline; 250 mg qid or 500 mg bid (between meals and at bedtime) should be continued for ≥ 4 wk and then decreased to the lowest effective dose. Occasionally the dosage must be increased to 500 mg qid. Because relapse ordinarily follows short-term treatment, therapy must be continued for months to years, although tetracycline 250 or 500 mg/day is often sufficient. Many dermatologists consider the more costly minocycline to be the systemic antimicrobial of choice because of its efficacy, lack of GI side effects, simplified dosing with regard to meals, and lack of photosensitization. Side effects include dizziness and pigmentation of the skin and mucous membranes. Other systemic antimicrobials that may be used include erythromycin and doxycycline. Both can cause GI side effects, and doxycycline is a frequent photosensitizer. Tetracycline should not be given at bedtime because of the risk of esophageal erosions. Full-dose systemic antibiotics (tetracycline 500 mg bid, minocycline 100 mg bid, doxycycline 100 mg bid, and erythromycin 333 mg tid) should be continued for ≥ 4 wk before tapering. Optimal therapeutic results are achieved in 6 to 12 wk.

The most common adverse effect of prolonged antibiotic use in women is candidal vaginitis. If local and systemic therapy do not eradicate this problem, antibiotic therapy for acne must be stopped. Long-term use of antibiotics may also produce a gram-negative pustular folliculitis around the nose and in the center of the face. This uncommon superinfection may be difficult to clear. It is best treated with oral isotretinoin after discontinuing the oral antibiotic.

Oral isotretinoin is the best treatment for patients in whom antibiotics are unsuccessful or in patients with very severe deep acne. This drug has revolutionized therapy for acne but should be used only by physicians who are familiar with its adverse effects. Because isotretinoin is teratogenic, women at risk of pregnancy must use 2 methods of contraception for 1 mo before taking the drug, while taking the drug, and at least 1 mo after discontinuing it. Pregnancy tests before beginning therapy and at monthly intervals are still recommended.

The dosage of isotretinoin is usually 1 mg/kg/day for 20 wk. In recalcitrant cases the dosage may be increased to 2 mg/kg/day. If side effects make this dosage intolerable, it may be reduced to 0.5 mg/kg/day. After therapy, acne may continue to improve. Most patients do not require a second course of treatment; when needed, it should be resumed only after the drug has been stopped for 4 mo. Re-treatment is required more often if the initial dosage is low (0.5 mg/kg/day). With this dosage (which is popular in Europe), fewer side effects occur; however, prolonged therapy is usually required.

Side effects occur in virtually all patients; the most common are dryness of conjunctivae and mucosae of the genitalia and chapped lips. Petrolatum usually alleviates mucosal and cutaneous dryness. Musculoskeletal symptoms (pain or stiffness of joints or of the lower back) occur in about 15% of patients. CBC, liver function, and triglyceride and cholesterol levels should be determined before treatment. Except for the CBC, each should be reassessed at 4 wk; unless abnormalities are noted, need not be repeated until the end of treatment. Tr

fective in comedonal or

(retinoic acid) in 0.025%, m, 0.05% limid, or 0.01% io often effective. A new apalene 0.1% gel, was re- he USA. It may be slightly topical tretinoin. These applied carefully and at ight if irritation is excess entire affected area only olabial folds, and crease d be avoided. The liquid hould be applied with a cator. Exposure to sun- r drugs are restricted to ation. With tretinoin or ay worsen at first; im equires ≥ 2 to 4 wk. s include 5% to 10% ben- drugs, and various sul- inations; they are usu- ly or one preparation in the morning. Oral ami- eipful in superficial pus-

orous management is residual scarring. For ns, topical treatment broad-spectrum oral effective because it re- anisms. The most cost- ine; 250 mg qid or 500 ioals and at bedtime) l for ≥ 4 wk and then rest effective dose. Do- e must be increased to relapse ordinarily fol- ment, therapy must be to years, although te- mg/day is often suffi- ologists consider the line to be the systemic ce because of its eff- effects, simplified dos- als, and lack of photo- ects include dizziness the skin and mucous stemic antimicrobials ude erythromycin and cause GI side effects. frequent photosensi- ould not be given at e risk of esophageal temic antibiotics (tet- minocycline 100 mg bid, doxycycline 100 mg bid, and erythromycin 333 mg tid) should be continued for ≥ 4 wk before tapering. Optimal therapeutic results are achieved in 6 to 12 wk.

The most common adverse effect of prolonged antibiotic use in women is candidal vaginitis. If local and systemic therapy does not eradicate this problem, antibiotic therapy for acne must be stopped. Long-term use of antibiotics may also produce a gram-negative pustular folliculitis around the nose and in the center of the face. This uncommon superinfection may be difficult to clear and is best treated with oral isotretinoin after discontinuing the oral antibiotic.

Oral isotretinoin is the best treatment for patients in whom antibiotics are unsuccessful or in patients with very severe deep acne. This drug has revolutionized therapy for acne but should be used only by physicians who are familiar with its adverse effects. Because isotretinoin is teratogenic, women at risk of pregnancy must use two methods of contraception for 1 mo before taking the drug, while taking the drug, and at least 1 mo after discontinuing it. Pregnancy tests before beginning therapy and at monthly intervals are still recommended.

The dosage of isotretinoin is usually 1 mg/kg/day for 20 wk. In recalcitrant cases, the dosage may be increased to 2 mg/kg/day. If side effects make this dosage intolerable, it may be reduced to 0.5 mg/kg/day. After therapy, acne may continue to improve. Most patients do not require a second course of treatment; when needed, it should be resumed only after the drug has been stopped for 4 mo. Re-treatment is required more often if the initial dosage is low (0.5 mg/kg/day). With this dosage (which is very popular in Europe), fewer side effects occur; however, prolonged therapy is usually required.

Side effects occur in virtually all patients; the most common are dryness of conjunctivae and mucosae of the genitalia and chapped lips. Petrolatum usually alleviates mucosal and cutaneous dryness. Musculoskeletal symptoms (pain or stiffness of large joints or of the lower back) occur in about 15% of patients. CBC, liver function, and triglyceride and cholesterol levels should be determined before treatment. Except for the CBC, each should be reassessed at 4 wk and, unless abnormalities are noted, need not be repeated until the end of treatment. Triglycerides rarely increase to a level at which the drug should be discontinued. Liver function is seldom affected.

For firm (cystic) acne lesions, injection of 0.1 mL **triamcinolone acetonide suspension** 2.5 mg/mL (the 10 mg/mL suspension must be diluted) into an inflamed cyst or abscess is helpful; local atrophy (resulting from the corticosteroid or destruction of tissue by the cyst) is usually transient. For isolated, very boggy lesions, incision and drainage are often beneficial but may result in residual scarring.

Dermabrasion for small scars is sometimes useful, but its permanent effect is controversial. X-ray therapy is not justified. Topical corticosteroids, especially if fluorinated, may worsen acne. When other measures fail and acne seems related to menses, an oral estrogen-dominant estrogen-progesterone–containing contraceptive may be tried; therapy ≥ 6 mo is needed to evaluate the effect.

ROSACEA

A chronic inflammatory disorder, usually beginning in middle age or later and characterized by telangiectasia, erythema, papules, and pustules primarily in the central areas of the face.

Tissue hypertrophy, particularly of the nose (rhinophyma), may result. Rarely, rosacea occurs on the trunk and extremities.

The cause is unknown, but the disease is most common in persons with a fair complexion. Diet probably plays no role in the pathogenesis. Rosacea may resemble acne, but comedones are never present; differential diagnosis also includes drug eruptions (particularly from iodides and bromides), granulomas of the skin, lupus erythematosus, and perioral dermatitis.

Treatment

Topical metronidazole gel or cream or broad-spectrum oral antibiotics are usually effective. Tetracycline 1 g/day in divided doses (between meals and in the evening) is most effective and has few side effects with long-term use. The dose should be reduced once a beneficial response is achieved. Often, 250 mg/day or every other day controls the disease. If tetracycline is ineffective or not tolerated, minocycline, erythromycin, and doxycycline are effective alternatives.

Recalcitrant cases often respond to oral isotretinoin (see ACNE, above). Topical fluorinated corticosteroids aggravate rosacea and are contraindicated. Surgical correction may be required for rhinophyma. Sunscreen use is recommended because sunlight may exacerbate rosacea.

PERIORAL DERMATITIS

A red papular eruption of unknown cause occurring around the mouth and on the chin.

The condition occurs predominantly in women aged 20 to 60. It may superficially resemble acne or rosacea. A zone of normal skin lies between the lesions and the vermilion border of the mouth. Topical corticosteroids worsen this disorder.

Treatment with tetracycline 1 g/day in divided doses (between meals) is often effective. The dose should be reduced gradually after 1 mo to the smallest effective dose. Patients with mild perioral dermatitis who are reluctant to take oral antibiotics may try topical metronidazole 0.75% gel or cream bid. Recalcitrant, disfiguring cases may clear with oral isotretinoin (see ACNE, above).

HYPERTRICHOSIS

(Hirsutism)

Excessive hair growth.

(See also ADRENAL VIRILISM in Ch. 9 and AMENORRHEA in Ch. 235.)

A familial tendency is common, and prevalence is greater in persons from Mediterranean areas. An endocrine disorder (adrenal virilism, basophilic adenoma of the pituitary, masculinizing ovarian tumors, Stein-Leventhal syndrome) may be implicated in women and children. Hypertrichosis also may occur in porphyria cutanea tarda.

It is frequent after menopause, with systemic androgenic steroid or corticosteroid therapy, with some antihypertensive drugs (eg, minoxidil), and with cyclosporine.

Treatment

Any underlying disorder should be treated. The only safe permanent local treatment is destruction of individual hair follicles either by electrolysis, which is tedious, or by laser (photodynamic therapy). Widely used temporary measures include plucking, shaving, and epilating wax. Chemical depilatories are acceptable if the directions are followed but may irritate skin. Hair bleach may mask the condition if the hair is fine. In women with certain endocrine abnormalities, an inhibitor of androgens (ie, an antiandrogen), such as spironolactone or cyproterone acetate, may be tried. A gynecologic endocrinologist should be consulted.

ALOPECIA

(Baldness)

Partial or complete loss of hair.

Alopecia may result from genetic factors, aging, or local or systemic disease. (Seborrheic dermatitis and psoriasis, the dermatoses that most commonly affect the scalp, very rarely produce alopecia.)

Nonscarring alopecia: Nonscarring (noncicatricial) alopecia occurs without gross atrophy. Male-pattern alopecia is extremely common. It is familial and requires the presence of androgens, but the cause is unknown. Hair loss begins in the lateral frontal areas or over the vertex. If onset is in the mid-teens, subsequent alopecia commonly is extensive. Female-pattern alopecia is common. It is confined ordinarily to thinning of the hair in the frontal, parietal, and crown regions; complete alopecia in any area is rare.

Toxic alopecia is usually temporary and may follow, by as long as 3 to 4 mo, a severe, often febrile illness (eg, scarlet fever). It may also occur in myxedema, hypopituitarism, or early syphilis; after pregnancy; and with some drugs, particularly cytotoxic drugs, thallium compounds, and overdoses of vitamin A or retinoids.

Alopecia areata is characterized by sudden hair loss in circumscribed areas usually in persons who have no obvious skin disorder or systemic disease. Any hairy area may be involved, the scalp and beard most frequently. Rarely, all body hair may be lost (alopecia universalis). The prognosis is poor if alopecia is extensive or begins before adolescence, but alopecia confined to a few areas is often reversed in a few months even without treatment, although recurrences are common. Antimicrosomal antibodies and antibodies to thyroglobulin, gastric parietal

cells, and adren
some cases.
Trichotilloma
rotic habit that u
it may remain un
Hairs may be br
lengths. Stubbly re
the condition is c
from alopecia are.
Scarring alop
alopecia results fr
sue destruction. I
rophy or scarring,
pected. In injuri
trauma, x-ray atrop
ring is usually app
Cutaneous lupus
planus, chronic de
fections, deep fac
(eg, sarcoidosis, sy
inflamed tinea ca
produce scarring a
ing tumors of the sc
with resultant sca
opecia is idiopathi

Diagnosis

A microscopic
hair allows an an
which may differen
scarring alopeci
provides useful di
quires experience a
(about 40 to 60 hai
the scalp should be
90% of hairs are
phase; the rest are
phase. Anagen hai
to their roots, when
sheaths and have
Postpartum and p
characterized by a
telogen hairs, whe
thallium or antimit
ized by a normal pe
The anagen hair in
break easily becau
Alopecia areata is c
look like exclamat
Biopsy of the
forms of alopecia
chotillomania). Hi
immunofluorescen
erythematosus, lic
planus of the scalp
astatic lesions, wh

EXHIBIT B

Histopathology of Rosacea

Ronald Marks, BSc, MBBS, MRCP, DTM&H, and
John Nigel Harcourt-Webster, MA (Camb) MB B Chir, MD, MC Path, London

Biopsies from 108 patients with rosacea have been examined and the histological changes correlated with the clinical condition. There is no single histological feature unique to rosacea but it is characterized by a combination of several histological signs; various types of rosacea represent an exaggeration of one or another aspect of the basic pathological changes; the disease is neither primarily a folliculitis nor an inflammatory disorder of small blood vessels. There is disorganization of the upper dermal connective tissue with edema, disruption of fibers, and frequently severe elastosis. A comparison of 39 rosacea patients with 39 controls for solar elastotic change indicated an increased incidence and degree of elastosis in rosacea patients. It is suggested that loss of integrity of upper dermal connective tissue may permit vascular dilatation and that this may have an important role in the pathogenesis of the disease.

THERE is little knowledge as to the etiology and pathogenesis of rosacea. Factors considered have included the seborrheic state, gastrointestinal disturbances, and psychological disorders (Beerman and Stokes,[1] and Hellier[2]) and the mite *Demodex folliculorum* (Ayres and Ayres[3]; Russell[4]; and Spickett[5]). The persistent erythema, the telangiectasia, and the facial flushing suggest that the small blood vessels of the face are involved either primarily or secondarily; Sobye[6] suggested that prolonged climatic exposure caused vascular injury.

A previous investigation indicated that edema and disorganization of the upper dermis were conspicuous histological features and that the degree of solar elastosis was excessive (Marks[7]). In this study we have examined biopsies from 108 patients with rosacea to further define the role of the above factors.

Patients

Biopsies were taken from 108 patients, special care being taken to record the type of lesion (Table 1). For the purpose of this study rosacea was defined as follows: A disease of the skin mostly affecting the cheeks and often the chin, nose, and forehead characterized by persistent erythema and often telangiectasia with acute episodes of edema, papules, and pustules in some cases. Patients with comedones, scars, or cysts were diagnosed as having acne even though there was a background of erythema, and excluded. Similarly patients with perioral dermatitis were not included. For evaluation of the degree of elastotic change, portions of skin were obtained from biopsies and excisions from patients with a variety of skin complaints undergoing routine minor surgical procedures matched for age, sex, and site of biopsy (Table 2). The following were the diagnoses in this control group: compound nevus, ten; seborrheic wart, six;

Table 1.—*Types of Rosacea in This Study*

	Papular	Erythemato-telangiectatic	Rosacea of Nose
Men	44	12	7
Av age, yr	50.5	47.5	56.3
Women	30	12	3
Av age, yr	48	432	47.6
Total No. of Patients	74	24	10

Accepted for publication July 15, 1968.

From St. John's Hospital for Diseases of the Skin, London (Dr. Marks), and the Department of Morbid Anatomy, St. George's Hospital, London (Dr. Harcourt-Webster).

Reprint requests to St. John's Hospital for Diseases of the Skin, Lisle St, Leicester Sq, London WC 2.

Table 2.—*Age and Sex, and Site of Biopsy of Matched Rosacea and Control Patients*

Patients	Av Age	Men	Women	Chin	Cheek	Forehead	Nose	Neck
Rosacea	48.4	13	26	4	18	11	5	1
Controls	49.3	11	28	4	15	13	6	1

Table 3.—*Results of Questionnaire**

Scoring System	Score
Occupation†	
Mostly (sometimes) outside more than 2 yr	2 (1)
Mostly (sometimes) outside more than 5 yr	5 (2)
Mostly (sometimes) outside more than 10 yr	10 (4)
Mostly (sometimes) outside more than 20 yr	20 (8)
Living in a sunny country	
2 - 5 yr	10
5 - 10 yr	20
More than 10 yr	30
Outdoor activities	
Keen on outdoor activities (in past)	5 (3)
Keen sunbather	6
Tans easily	−5
Burns easily	2

The mean score for the rosacea patients was **7.91** and the mean score for the controls was **12.07**.

Complexion, Hair and Eye Color in Rosacea and Control Patients

Complexion	*Rosacea*	Controls
Light	12	15
Medium	23	14
Dark	0	1
Hair		
Light	8	11
Medium	19	13
Dark	8	6
Eyes		
Light	23	18
Medium	2	0
Dark	10	12

* Thirty-five rosacea patients and 30 controls replied to the questionnaire.

† *Exposure:* With regard to exposure the questions concerned occupation, periods spent in a sunny country, and other outdoor activities and preferences. A scoring system was used to evaluate the degree of exposure.

Table 4.—*Results of Comparison of Matched Rosacea and Control Sections for Elastosis*

No. of Specimens	Score 0	+1	−1	+2	−2	Total Points
9	X					0
9		X				+9
2			X			−2
12				X		+24
7					X	−14
Total for all matched specimens						+17

basal cell epithelioma, ten; keratoacanthoma, three; pyogenic granuloma, one; cyst, one; lentigo, one; sebaceous gland hypertrophy, one; benign warty hyperplasia, one; hemangioma, one; nevus sebaceous, one; and lupus erythematosus, one. Thirty-nine such matched specimens were obtained. Information concerning occupation, exposure to the sun, residence in sunny countries, and skin coloring was obtained by a questionnaire completed by the patients (Table 3). There was a higher estimated exposure in the control group but the coloring of the two groups was approximately similar.

Methods

Biopsies were taken after local infiltration with 1% lidocaine. An ellipse of skin, approximately 1 × 0.5 cc, was surgically removed and fixed in 10% formol saline. Seventy five specimens were sectioned routinely. Serial sections were cut from 24 specimens of papular or papulopustular lesions, eight of these at 20μ intervals being mounted. A further seven specimens were sectioned obliquely to show the epidermis, upper dermis, and hair follicles, another two were cut horizontally at various levels to show numerous follicles in cross section.

All sections were stained with hematoxylin and eosin. Sections from 11 unmatched rosacea patients and all the sections from the 39 matched rosacea and 39 control patients were stained with the Verhoeff's technique for elastic tissue.

Evaluation of the Amount of Solar Elastosis

Solar elastosis was identified in the hematoxylin and eosin stained sections as altered dermal connective tissue in the papillary and upper dermis; this appeared either fragmented and disorganized or gave a homogenized appearance and tended to be more basophilic than the surrounding dermis. The degree of elastotic degeneration in sections from rosacea patients and controls was compared by directly contrasting paired sections from each group matched for age, sex, and site of biopsy. The following scoring system was devised.

0, No difference in the degree and extent of elastosis in the two section.

+1, Slight
section.
−1, Slight
section.
+2, More
the rosacea t
−2, More
the control s
The findin
are given in

Papular R
papulopustul
tained.

Inflammat
nous feature
amount of in
upper and n
lymphocytes
portions. Son
erable numbe
cytes, plasm
cells of a fon
nolated but
eign materia
tions; in ne
numbers (Fi
a loosely arr
a particular
eight section
type. In gen
papules ther
with a more
In six biops
small papule
was a small
cytic infiltrat

Pilosebacec
uterum.—Am
showed an
licle. In ten
of the follic
phonuclear l
stance of the
ruption was
was the histo
tular lesions
five, however,
the follicle w
inflammatory
dence as to
event.

+1, Slightly more elastosis in the rosacea section.

−1, Slightly more elastosis in the control section.

+2, More than twice as much elastosis in the rosacea than the control section.

−2, More than twice as much elastosis in the control than in the rosacea section.

The findings of this comparison technique are given in Table 4.

Observations

Papular Rosacea.—Biopsies of papules or papulopustules from 74 patients were obtained.

Inflammatory Cell Infiltrate.—A conspicuous feature was the presence of a variable amount of inflammatory cell infiltrate in the upper and middermis consisting mainly of lymphocytes and histiocytes in varying proportions. Some sections also included considerable numbers of polymorphonuclear leukocytes, plasma cells, and giant cells. Giant cells of a foreign-body type which were vacuolated but contained no recognizable foreign material were seen in 11 (14%) sections; in one section they were seen in great numbers (Fig 1). The infiltrate was usually a loosely arranged collection of cells without a particular pattern (Fig 2); however, in eight sections (11%) it was of tuberculoid type. In general, in the larger and older papules there was more cellular infiltrate with a more organized type of arrangement. In six biopsies taken from newly formed small papules the only conspicuous feature was a small amount of perivascular lymphocytic infiltrate.

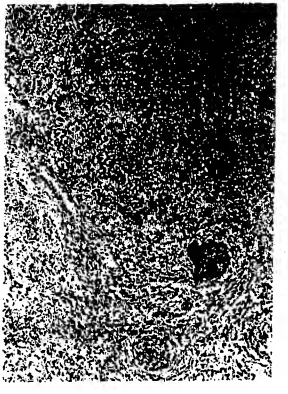
Pilosebaceous Apparatus: Demodex Folliculorum.—Among the 74 biopsies, 15 (20%) showed an abnormality of the hair follicle. In ten there was partial disruption of the follicular epithelium and polymorphonuclear leukocyte invasion of the substance of the pilosebaceous unit. This disruption was usually high in the follicle and was the histological counterpart of the pustular lesions noted clinically (Fig 3). In five, however, there was total destruction of the follicle with an intense granulomatous inflammatory reaction but there was no evidence as to th agent responsible for this event.

Of the 24 specimens serially sectioned six (25%) showed areas of acute folliculitis, while in the remainder the inflammation was entirely independent of the pilosebaceous apparatus. In the seven biopsies cut obliquely and in the two cut horizontally there was no primary abnormality of the numerous pilosebaceous units seen.

With 37 specimens (51%) the infiltrate was partially distributed around the hair follicles, and often the perifollicular localization appeared incidental to the cells collecting perivascularly in the right perifollicular plexuses (Fig 4).

Fourteen biopsies (19%) contained recognizable parts of the mite demodex folliculorum in the lumina of the follicles. No other abnormal feature was seen in these sections and it was particularly noticed that only one of the infested follicles showed a folliculitis; there was no evidence that the demodex had penetrated the follicular epithelium. Fifty-eight biopsies (78%) showed follicular plugging with a loose meshwork of keratin.

Fig 1.—Papular rosacea with heavy chronic inflammatory infiltrate including numerous giant cells (hematoxylin and eosin, × 100).



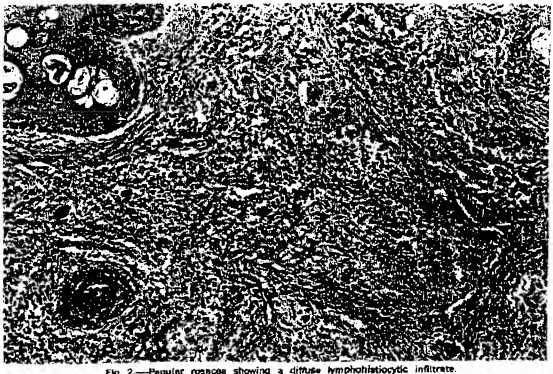


Fig 2.—Papular rosacea showing a diffuse lymphohistiocytic infiltrate. Note nearby uninvolved hair follicle. (hematoxylin and eosin, X 200).

Fig 3.—Papulopustular rosacea with an abscess containing many polymorphonuclear leukocytes high in the wall of the follicle. There is also a Demodex deeper down in the follicle, away from the inflammation (hematoxylin and eosin, X 100).

The Vessels.—Sixty-three sections (85%) included a pronounced vascular dilatation; this was very marked in 14 (21%). The greatest dilatation of the vessels occurred in the upper and papillary dermis, some vessels being of enormous size. Some of the vascular channels were lymphatics but in general these were more obvious in the middermis rather than in the upper dermis and papillae. The dilated vessels were often found amid edematous, disrupted, and elastotic connective tissue (see below). Only one specimen showed evidence of blood vessel damage with several vessels showing eosinophilic smudging of outline and endothelial cell swelling.

The inflammatory infiltrate was predominantly perivascular in 19 (26%) (Fig 5) and was partially perivascular in a further 42 sections (57%) loosely set in edematous tissue.

Epidermis.—In four sections there were

Fig 4. flammat

Fig 4.—Biopsy of patient with papular rosacea. There is a predominantly perivascular inflammatory infiltrate which also surrounds one follicle (hematoxylin and eosin, × 25).

Fig 5.—Early papular rosacea with a moderate perivascular chronic inflammatory cell infiltrate (hematoxylin and eosin, × 400).

papillary der-
sels being of
Some of the
els were lym-
general these
vious in the
ther than in
lis and papil-
l vessels were
id edematous,
elastotic con-
(see below).
imen showed
blood vessel
everal vessels
philic smudg-
nd endotheli-
r.
natory infil-
redominantly
1 19 (26%)
vascular in a
ly set in ede-

s there were

small foci of parakeratosis, in one there was moderate hyperkeratosis, and in another mild epidermal atrophy.

Erythematotelangiectatic Rosacea.—Biopsies from 24 patients with persistent erythema and telangiectasia and a variable amount of swelling were examined. The histological changes in general resembled those of the papular type of rosacea. However, the cellular infiltrate was mainly perivascular and the predominant cell type was the lymphocyte.

The most striking feature was a vascular dilatation which was very pronounced in nine (38%) (Fig 6). In these patients with very obvious telangiectasia, clinically there was a corresponding dilatation of vessels in their biopsy sections. Most of these dilated channels were in the upper dermis which also showed disruption of connective tissue architecture. The upper dermis was reduced in bulk, edematous, and frag-

Fig 6.—Erythematotelangiectatic rosacea showing grossly dilated and irregular vascular channels in the upper dermis. There is also solar elastosis and some disruption of the normal connective tissue (hematoxylin and eosin). × 100).

Fig 7.—Erythematotelangiectatic rosacea showing prominent solar elastosis and telangiectasia (hematoxylin and eosin, × 200).

mented with
loosely stru
elastosis was
ture (Fig 7

Results o
toids.—From
more elastos
ces patients
controls ha
rosacea gro
icance to th
(uncontrolle
on a total
severe degre
only nine fa
change.

Other Cl

Swollen, r
were biopsie
degree of r
early exam
showed a p
nine there
was severe i
inflammator
fusely scatte
upper dermi
few small cl
kocytes with
cles. Four o
to moderat
hypertrophy.

Facial ede
the patients
cially noted
patients show
though eden
spicuous. In
the small blo
another ther
tous cellular
of the vascul
ic) in the de

The chin
thickened an
thickening s
ay there was
hyperplasia,
sis, there wa
lymphocytes
mild erythe
had swollen

n the upper
tion of con-
pper dermis
a, and frag-

grosa-
upper
uption
osin).

mented with attenuated strands of collagen loosely strung between the vessels. Solar elastosis was a prominent accompanying feature (Fig 7) (see below).

Results of Comparison for Degree of Elastosis.—From Table 4 it may be seen that more elastotic change was found in the rosacea patients rather than in the controls. The controls had more sun exposure than the rosacea group and this gives added significance to these results. Another assessment (uncontrolled) of elastosis was performed on a total of 104 biopsies; 33 showed a severe degree of elastotic degeneration while only nine failed to show any evidence of this change.

Other Clinicopathological Correlations

Swollen, reddened noses from ten patients were biopsied. None of these had a severe degree of rhinophyma but were chosen as early examples of this process. All ten showed a pronounced telangiectasia and in nine there was elastotic degeneration that was severe in three. There was also a heavy inflammatory cell infiltrate which was diffusely scattered through the middermis and upper dermis. In two sections there were a few small clusters of polymorphonuclear leukocytes with invasion of nearby hair follicles. Four of these sections showed a mild- to moderate degree of sebaceous gland hypertrophy.

Facial edema was a feature of several of the patients in this series but it was especially noted in five. Sections from these patients showed no distinguishing features although edema and telangiectasia were conspicuous. In one there was reduplication of the small blood vessel endothelium while in another there appeared to be a granulomatous cellular infiltrate in the lumina of some of the vascular channels (possibly lymphatic) in the deeper part of the dermis.

The chin of one patient was diffusely thickened and was reminiscent of the nasal thickening seen in rhinophyma. In the biopsy there was conspicuous sebaceous gland hyperplasia, telangiectasia, and solar elastosis, there was also a scattered infiltrate of lymphocytes and histiocytes. A patient with mild erythematotelangiectatic rosacea also had swollen reddened earlobes for many years; a biopsy from one of these showed pronounced edema and telangiectasia throughout the dermis and a small amount of inflammatory cell infiltrate.

Two sections were available from patients who had used potent corticosteroid preparations topically, they presented with a very striking persistent facial redness and telangiectasia as described by Sneddon (1969).[9] Telangiectasia and loss of normal architecture in the upper dermis were prominent features of these sections.

Comment

There are few reports of the histological changes in rosacea and little attempt has been made to correlate such changes with clinical findings. The available literature deals mainly with the granulomatous nature of the inflammatory infiltrate and its occasional tuberculoid arrangement (Laymon and Schoch[9]; Laymon[10]; Michelson[11]; and Van Ketel[12]). Miescher[13] found that 64% of a series of 58 cases of papular rosacea included tuberculoid-type infiltrates, and he divided rosacea into erythematous, telangiectatic, a glandular hyperplastic type leading to rhinophyma and a micronodular form associated with acneiform papules.

Histological Diagnosis of Rosacea

The most common features seen in biopsy material from all clinical types of rosacea are: a variable amount of lymphohistiocytic inflammatory infiltrate arranged loosely around the upper dermal blood vessels, telangiectasia, edema, elastosis, and disruption of the architecture of the upper dermis. These features in combination should suggest a histological diagnosis of rosacea. More extensive and dense inflammatory cell infiltrates with numerous histiocytes and occasional giant cells may indicate papular rosacea, while a pronounced upper dermal dystrophy and telangiectasia suggests the erythematotelangiectatic variety.

Pathogenetic Considerations

Role of the Hair Follicle.—Only 20% of the material from our patients with papular rosacea showed disruption of hair follicles. Our findings strongly suggest therefore, that

there is no basic follicular abnormality in rosacea. Two thirds of this 20% had a small abscess in the upper part of the follicle corresponding to the clinical feature of pustulation. The remaining one third showed a more profound destruction of follicular structure with a resultant granulomatous inflammatory reaction; this may represent a healing stage of pustular folliculitis. Pustulation is considered to be a secondary phenomenon because of the small number of cases in which it was seen and because it was only detected in sections from patients with papular rosacea where there appeared to be other more profound and commonly seen changes. In many sections the perivascular inflammatory infiltrate in the perifollicular plexuses created a false appearance of folliculitis.

Role of *Demodex*.—The mite *D folliculorum* is thought to occur more frequently in rosacea patients than in normal population (Russell[4] and Spickett[5]). However, the mite is commonly found in other facial dermatoses. The finding of *Demodex* in only 19% of our biopsy material and its absence from areas of inflammation in sections in which it was found are much against a significant role for this organism in this disease. A granulomatous tissue reaction to *D folliculorum* is known to occur in the marsupial mouse (Nutting and Beerman[14]) and in other animals (Nutting[15]). However, there was no suggestion that the human variety of *D folliculorum* was responsible for such a reaction in our material. It is possible that a local delayed hypersensitivity response to *Demodex* antigens diffusing through the intact follicular epithelium is partly responsible for the inflammatory component of the disease but one would expect that all follicles containing the mite would show inflammation and this is not seen. However, until suitable antigens are available this hypothesis cannot be tested.

Role of the Small Vessels.—In this study there is no evidence that primary vascular damage occurs in rosacea. The peripheral lesions of disseminated rosacea may include damage to small blood vessels with entothelial cell swelling and even fibrinoid degeneration (Marks and Wilson-Jones[16]). No comparable lesions were seen in the facial lesions of this series. Apart from the above considerations there is the functional adequacy of the vessels to be considered. This process of upper dermal disorganization could account for the erythema and telangiectasia which are cardinal clinical features of rosacea. It is a common clinical observation that the cheeks are cool in a rosaceous subject and this has been confirmed by direct thermometry (Borrie[17]). Although there are no published quantitative observations it seems probable that the congestion of the dermal blood vessels is associated with a slow ambient flow of blood. The sluggish circulation is probably due to pooling in the enormously dilated vascular channels of the subpapillary venous plexus. The vascular dilatation is not due to intrinsic disease of the vessels but appears to be due to lack of a surrounding firm connective tissue framework allowing passive dilatation.

Clinical aspects of rosacea such as swelling of the affected areas and even pronounced lymphoedema are reflected in histological sections as edema and lymphatic dilatation. The dilated lymphatics may be the result of the same dermal dystrophy as causes the telangiectasia; the edema could result from their loss of efficiency as conduits.

Role of Solar Elastosis and Climatic Factors.—Solar elastosis appeared to be more frequent and of greater severity in rosacea patients than in controls. This confirms the impression gained previously (Marks[7]) that the histological change of elastotic degeneration was more obvious in patients with rosacea. No explanation for this observation is forthcoming from our observations. It is suggested that the elastosis contributes to the disorganization seen in the upper dermis.

Patients with rosacea often complain of burning and soreness when in the sun; 23% complained that the sun made them worse although increased sensitivity to ultraviolet light was not found (Marks[7]). In addition, the disease appears to be more common in subjects with fair complexions. Harthausen[13] believed that climatic exposure was important in its etiology. Søbye[6] and Brodthagen[12] were also impressed with the role of exposure to the sun in the development of rosacea. It is possible that patients with this disease are more susceptible than normal to climatic stimuli and that the upper dermal changes are a result of their continued action.

tional ade-
dered. This
organization
and telan-
cal features
al observa-
a rosaceous
med by di-

Although
ive observa-
congestion
associated
blood. The
lue to pool-
acular chan-
plexus. The
to intrinsic
s to be due
connective
e dilatation,
ch as swell-
even pro-
ted in histo-
lymphatic
may be the
hy as causes
could result
nduits.
limatic Fac-
to be more
in rosacea
onfirms the
farkt') that
ic degenera-
s with rosa-
eervation is
ns. It is sug-
utes to the
e dermis.
comolain of
ne sun; 28%
them worse
ultraviolet
In addition,
common in
Harthausen[18]
as important
hagen[19] were
exposure to
osacea. It is
disease are
limatic stim-
hanges are a

Rosacea of the Nose

The early examples of rosacea affecting the nose demonstrate changes similar to other types of rosacea; sebaceous gland hypertrophy is not a prominent feature. Acker and Helwig[20] in a review of the histology of 47 cases of rhinophyma found five with a basal cell epithelioma. Forty-one of the 47 showed sebaceous gland hypertrophy and one third showed telangiectasia. Rhinophyma with its enormous proliferation of sebaceous glands may represent the late changes of rosacea affecting the nose. One of our sections was derived from a man with an irregularly swollen, dark red chin that was reminescent of rhinophyma. Interestingly it showed a moderate degree of sebaceous gland hypertrophy as well as a considerable amount of inflammatory cellular infiltrate, telangiectasia, and elastosis. A similar but more severely affected patient—a woman, was described by Sams.[21]

It is possible to draw several important conclusions from our findings in this study: (1) There is no single histological feature unique to rosacea, but a combination of several findings makes this a likely diagnosis. (2) The different clinical types represent an exaggeration of one or another aspect of the basic histology. (3) There is no evidence from the histological material examined that the disease is either primarily a disorder of the pilosebaceous apparatus, or an inflammatory disorder of small blood vessels. (4) A prominent component of the histopathology of rosacea, observed in this study, was disorganization in the upper dermis.

Drs. S. C. Gold and K. V. Sanderson of St. George's Hospital allowed us to study their patients. The physicians of St. John's Hospital referred patients to us for study. Mr. F. Hammond, Mr. R. Truman, and Mr. P. Manning of the Department of Morbid Anatomy, St. George's Hospital, gave technical assistance.

References

1. Beerman, H., and Stokes, J.H.: Rosacea Complex and *Demodex folliculorum*, *Arch Derm Syph* 29:874-884, 1934.
2. Hellier, F.F.: Rosacea and Acne, *Brit Med J* 2:1053-1055 (Oct 26) 1946.
3. Ayres, S., Jr., and Ayres, S., III: Demodactic Eruptions Demodicidosis, *Arch Derm* 83:154-165 (May) 1961.
4. Russell, B.F.: Some Aspects of the Biology of the Epidermis, *Brit Med J* 1:815-820 (March 24) 1962.
5. Spickett, S.G.: Etiology of Rosacea, letter, *Brit Med J* 1:1625-1626 (June 9) 1962.
6. Sebys, P.: Etiology and Pathogenesis of Rosacea, *Acta DermatoVener* 30:137-158 (Feb) 1950.
7. Marks, R.: Concepts in the Pathogenesis of Rosacea, *Brit J Derm* 80:170-177 (March) 1968.
8. Sneddon, I.: Adverse Effect of Topical Fluorinated Corticosteroids in Rosacea, *Brit Med J* 1:671-673 (March 15) 1969.
9. Laymon, C.W., and Schoch, E.P.: Micropapular Tuberculid and Rosacea, *Arch Derm Syph* 58:286-300 (Sept) 1948.
10. Laymon, C.W.: Lupoid Rosacea, *Arch Derm Syph* 63:409-418 (April) 1951.
11. Michelson, H.E.: Does the Rosacea-like Tuberculid Exist?, *Arch Derm* 78:681-686 (Dec) 1958.
12. Van Ketel, W.G.: Rosacea-like Tuberculid of Lewandowsky, *Dermatologica* 116:201-210, 1958.
13. Mescher, G.: Rosacea und Rosacea-ähnliche Tuberkulida, *Dermatologica* 88:150-170 (July) 1943.
14. Nutting, W.B., and Beerman, H.: Atypical Giant Cells in Anticlinos Sinarii Due to Demodicid Mites, *J Invest Derm* 45:504-506 (June) 1965.
15. Nutting, W.B.: Demodicidae-Status and Prognostics, *Acrologia* 6:441-454.
16. Marks, R., and Wilson-Jones, E.: Disseminated Rosacea, *Brit J Derm* 81:15-29 (Jan) 1969.
17. Bozzie, P.: The State of Blood Vessels of the Face in Rosacea: I. *Brit J Derm* 67:5-8 (Jan) 1955.
18. Harthausen, H.: Changes in the Skin Vessels From Protracted Action of Climatic Factors and Their Significance in Various Skin Diseases, *Brit J Derm* 42:105-125 (March) 1930.
19. Brodthagen, H.: Mepacrine and Chloroquine in the Treatment of Rosacea, *Brit J Derm* 67:421-425 (Dec) 1955.
20. Acker, D.W., and Helwig, E.B.: Rhinophyma With Carcinoma, *Arch Derm* 95:250-254 (March) 1967.
21. Sams, W.M.: Rhinoptyma With Unusual Involvement of the Chin, *Arch Derm Syph* 26:834-837, 1932.